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Development of anti-velaglucerase alfa antibodies in clinical trial-treated patients with Gaucher disease

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ABSTRACT

Anti-drug antibodies may develop with biological therapies, possibly leading to a reduction of treatment efficacy and to allergic and other adverse reactions. Patients with Gaucher disease were tested for anti-drug antibodies every 6 or 12 weeks in clinical studies of velaglucerase alfa enzyme replacement therapy, as part of a range of safety endpoints. In 10 studies between April 2004 and March 2015, 289 patients aged 2–84 years (median 43 years) were assessed for the development of anti-velaglucerase alfa antibodies. Sixty-four patients were treatment-naïve at baseline and 225 patients were switched to velaglucerase alfa from imiglucerase treatment. They received velaglucerase alfa treatment for a median of 36.4 weeks (interquartile range 26.4–155.4 weeks). Four patients (1.4%) became positive for anti-velaglucerase alfa IgG antibodies, two of whom had antibodies that were neutralizing in vitro, but there were no apparent changes in patients' platelet counts, hemoglobin levels or levels of CCL18 and chitotriosidase, suggestive of clinical deterioration after anti-velaglucerase alfa antibodies were detected, and no infusion-related adverse events were reported. Less than 2% of patients exposed to velaglucerase alfa tested positive for antibodies and there was no apparent correlation between anti-velaglucerase alfa antibodies and adverse events or pharmacodynamic or clinical responses.

1. Introduction

Gaucher disease (GD) is an inherited metabolic disorder characterized by a deficiency of the lysosomal enzyme β-glucocerebrosidase, which results in the accumulation of glucocerebroside in macrophages throughout the body. GD is classified into three clinical subtypes based on the absence (type 1) or the presence and severity of central nervous system manifestations (types 2 and 3). The non-neuronopathic manifestations observed in all clinical subtypes include thrombocytopenia, anemia, splenomegaly, hepatomegaly and diverse pathological changes in bone and bone marrow [1].

Long-term enzyme replacement therapy (ERT) with exogenous glucocerebrosidase has been shown to be effective for the systemic features of GD [2–5]. Velaglucerase alfa is the only ERT preparation that is produced in a human cell line and, like the first placental-derived enzyme (alglucerase), it has an amino acid sequence identical to the naturally occurring human glucocerebrosidase [6]. To date, ERT with velaglucerase alfa has been studied in over 300 patients in six interventional clinical trials, three extension studies and an investigational new drug treatment protocol, providing longitudinal data of up to 7 years [7–17]. The other enzymes, imiglucerase and taliglucerase alfa, are manufactured differently, using non-human mammalian and plant cell lines in culture, respectively. Their amino acid sequences are not identical to the natural human enzyme. Moreover, there are apparent structural differences in the glycosylation patterns of these enzymes, although the clinical significance of this is uncertain [2,18–20].

Abbreviations: ADA, anti-drug antibody; AE, adverse event; CCL18, chemokine (C-C motif) ligand 18; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; ERT, enzyme replacement therapy; GD, Gaucher disease; RIP, radioimmunoprecipitation; TEAE, treatment emergent adverse event.

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Anti-drug antibodies (ADAs) are known to develop with biological therapies, which may lead to a reduction of treatment efficacy and the occurrence of allergic and other adverse reactions [21]. ADAs have been reported in 15% of patients with type 1 GD receiving imiglucerase during the first year of treatment; patients testing positive for anti-imiglucerase antibodies may be more likely to have hypersensitivity-type reactions [22]. ADAs have also been reported in patients with type 1 GD treated with taliglucerase alfa; 13 to 53% of patients in clinical studies tested positive [4]. Because ADA test results may be affected by assay methodology, underlying diseases, concomitant medications and other factors, frequencies of seroconversion (i.e., development of antibodies) between products may not be comparable [4].

The immunogenic potential of therapeutic proteins is dependent on many product-specific factors, including protein sequence or post-translational modifications, and host-specific factors [23–25]. Correlations have been observed between lysosomal storage disease genetic mutations, endogenous enzyme activity levels in patients with lysosomal storage diseases, and the development of neutralizing ADAs to exogenous therapeutic enzymes [26].

Patients were tested for anti-velaglucerase alfa antibodies throughout the velaglucerase alfa GD clinical study program as part of a wide range of safety endpoints. We have calculated the percentage of patients who developed anti-velaglucerase alfa antibodies in the clinical study program and evaluated the clinical and pharmacodynamic responses in these patients.

2. Methods

Ten clinical studies conducted between April 2004 and March 2015 were included in this analysis: six clinical trials, an expanded access treatment protocol and three extension studies (Fig. 1) [7,8,10–17]. All studies were conducted in accordance with ICH Good Clinical Practice guidelines and local regulations, and written informed consent was obtained from all patients.

Patients with a diagnosis of GD aged at least 2 years (or at least 18 years in the phase I/II trial) received ERT as a 60-min intravenous enzyme infusion, administered every other week by a healthcare professional. Except for one comparator arm that received imiglucerase in a non-inferiority trial, all patients in velaglucerase alfa studies were assigned and received velaglucerase alfa at a dose between 15 and 60 U/kg.

Pre-medications such as antihistamines and corticosteroids, to prevent or mitigate potential infusion-related reactions, were allowed in patients who were pre-medicated during their previous imiglucerase treatment and as needed, e.g., in patients experiencing recurrent infusion-related reactions.

2.1. Study assessments

In the velaglucerase alfa clinical studies, blood was sampled every 2–12 weeks to measure the hemoglobin concentration and platelet count. In all studies except the treatment access protocol (HGT-GCB-058), blood was also sampled (every 2–25 weeks) for plasma biomarker assays. The only study objective of HGT-GCB-058 was to assess the safety of velaglucerase alfa, so indicators of efficacy, like biomarkers, were not measured (hematology testing in HGT-GCB-058 was part of the safety evaluation).

Patients were monitored for adverse events (AEs) throughout the studies and required to undergo a range of safety assessments including physical examinations, measurement of vital signs at infusion visits, hematology and clinical chemistry tests and serum ADA testing.

Other assessments were conducted in the velaglucerase alfa clinical studies which are not included in this analysis but are described elsewhere [7,8,10–16,27].

2.2. Antibody testing

Serum samples were assessed for anti-velaglucerase alfa antibodies at Shire (Bioanalytical and Biomarker Development Department),

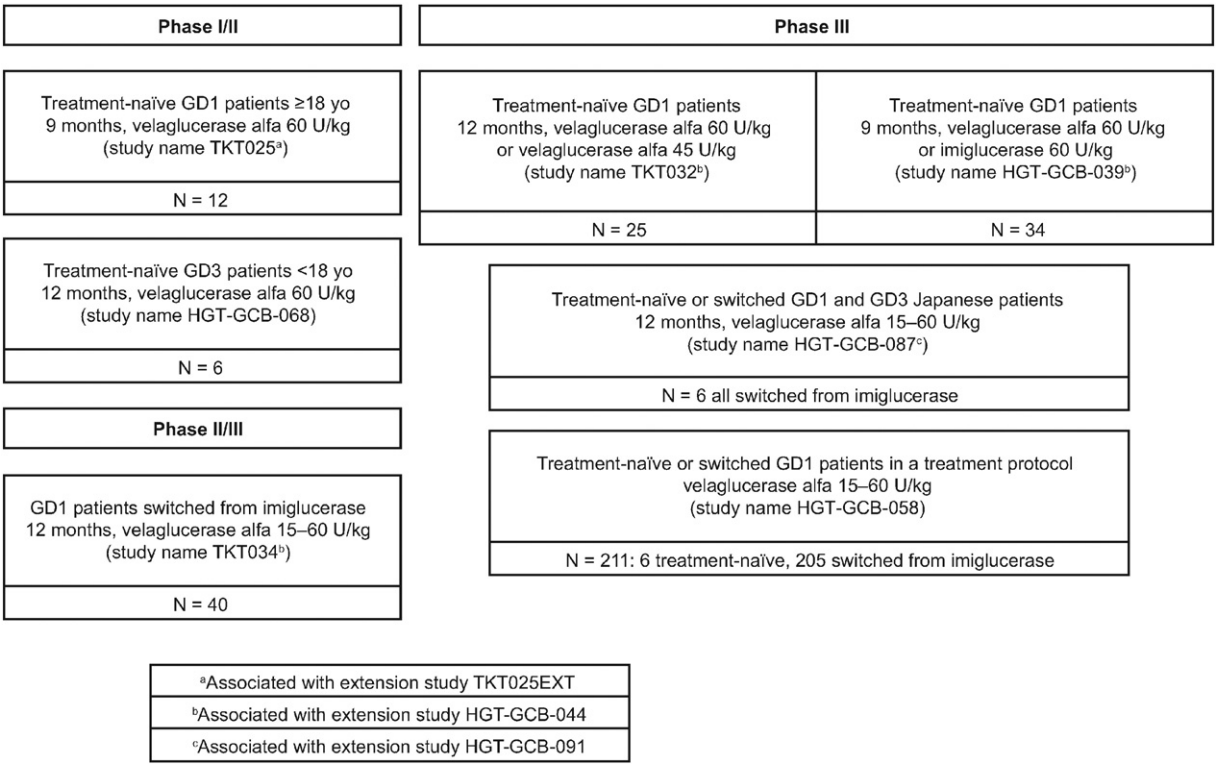

Fig. 1. Study designs and safety populations in velaglucerase alfa clinical studies to date. Treatment-naïve = patient who had never received ERT or any GD-specific treatment or was considered naïve because they had not received a GD-specific treatment for at least 12–30 months. GD1, type 1 Gaucher disease; GD3, type 3 Gaucher disease; yo, years old.

except in one trial (HGT-GCB-068) and in one extension study (HGT-GCB-091), wherein samples were analyzed at a contract research laboratory designated by Shire (Tandem Labs, A LabCorp Company, West Trenton, NJ, USA), following a decision made by Shire in 2013 to outsource patient sample testing [8,28,29]. Details of the methods used at the Shire Bioanalytical and Biomarker Development laboratory for the earliest, phase I/II studies (TKT025 and TKT025EXT) and for subsequent studies have been published [8,28].

Samples were taken at screening or baseline and then approximately every 6 or 12 weeks. To screen for the presence of anti-velaglucerase alfa antibodies, electrochemiluminescence (ECL) bridging assays were used, except in the earliest, phase I/II clinical trials in which an enzyme-linked immunosorbent assay (ELISA) format was used (ELISA was used only in TKT025 and TKT025EXT; the switch to the ECL method improved throughput and brought the assays up to industry standards at the time).

Samples that were positive on screening underwent additional testing. The confirmatory methods described here relate to the studies in which there were positive screening tests. In the treatment access protocol HGT-GCB-058 and the extension study HGT-GCB-044, the confirmatory tests were a radioimmunoprecipitation (RIP) assay for IgG antibodies and an ECL assay for IgE antibodies. In HGT-GCB-044, ECL assays for IgM and IgA antibodies were conducted as well. Antibody titers (in ng/mL) for confirmed positive samples were determined from the calibration curves run on the same plates in the bridge assay. In trial HGT-GCB-068, the confirmatory step was a drug competition format using ECL; isotypes were not determined and titers were reported as the maximum dilution factor by which a sample could be diluted and remain positive (signal above the assay cut point). The confirmatory testing was different in HGT-GCB-068 because when antibody testing was outsourced to a contract research laboratory, the ADA testing scheme was made simpler and thus more suitable for routine patient care. The new methods are at least as sensitive as the previous Shire methods and ADA testing results from these two testing facilities are highly comparable to each other based on a bridging study [29].

Samples confirmed as positive for anti-velaglucerase alfa antibodies were analyzed for neutralizing activity using a neutralizing antibody assay.

Patients were tested for anti-imiglucerase antibodies at screening or baseline in five of the six clinical trials, in the extension study HGT-GCB-044 (patients who had completed study HGT-GCB-039), and in the treatment access protocol. Patients in the clinical trial HGT-GCB-068 were not tested for anti-imiglucerase antibodies because the whole study population had never been exposed to imiglucerase. The antibody detection methods for anti-velaglucerase alfa antibodies and anti-imiglucerase antibodies were analogous.

2.3. Analysis and summary

Patients with antibody assessments conducted at baseline and at least once after baseline were included in this analysis. No statistical tests were performed.

Serial measurements of hemoglobin concentration, platelet count and the disease biomarkers chemokine (C–C motif) ligand 18 (CCL18) and chitotriosidase were plotted for each patient who tested positive for anti-velaglucerase alfa antibodies, to look for trends in the clinical and pharmacodynamic responses before and after antibodies were detected. Chitotriosidase values were normalized, as previously described [12,14], in patients found to have a common 24-base pair duplication in one copy of their chitotriosidase gene which results on average in a 50% reduction in activity [30].

Adverse event listings were reviewed for infusion-related reactions and other treatment-emergent adverse events (TEAEs). Infusion-related reactions were defined as AEs that began within 12 h of the start of the infusion and were judged as possibly or probably related to the study drug.

Table 1
Patients who developed anti-velaglucerase alfa antibodies.

Study name	Age at start of velaglucerase alfa treatment (years)	Sex	GD type	Velaglucerase alfa dose (U/kg)	Treatment before starting velaglucerase alfa	Anti-imiglucerase antibodies at baseline	Anti-velaglucerase alfa antibodies					
							First positive test (study week)	Subsequent positive tests (study week)	IgG	IgE	IgM and IgA	Neutralizing activity
HGT-GCB-068	3 years	Male	Type 3	60	Treatment-naïve	Not tested	Week 13	25, 37, 53/EOS	Isotyping not done			Sera negative
TKT034 and EXT	12 years	Female	Type 1	34	Imiglucerase (92 months)	Yes	Week 77	89, 101, 113, 125, 137, 149, EOS	Positive	Negative	Negative	Sera positive
TKT032 and EXT	26 years	Male	Type 1	45[a]	Treatment-naïve	No	Week 53	65, 77, 89[b]	Positive	Negative	Negative	Sera positive
HGT-GCB-058	68 years	Male	Type 1	30	Imiglucerase (103 months)	Yes	Week 13	25[c]	Positive	Negative	Not tested	Sera negative

EXT, extension study (HGT-GCB-044); EOS, end of study.
[a] Dose was adjusted during the extension study within the range of 15 to 60 U/kg.
[b] IgG negative at all subsequent assessments (week 101 to 233 and EOS).
[c] Last infusion received in week 33.

We also descriptively summarized data in patients who were found to have anti-imiglucerase antibodies that cross-reacted with velaglucerase alfa.

3. Results

In the clinical studies, 333 patients received at least one full or partial dose of velaglucerase alfa. In total, 289 patients exposed to velaglucerase alfa were assessed for the development of anti-velaglucerase alfa antibodies (i.e., assessed at baseline and at least once afterwards, before discontinuing from study) and included in this analysis, comprising 142 male and 147 female patients. The patients were aged between 2 and 84 years at baseline (median 43 years).

Of 289 patients, 281 had a diagnosis of type 1 GD; however, of these, two were subsequently found to be carriers (i.e., only one disease allele has been identified) [10]. Eight patients from two studies had type 3 GD (Fig. 1).

Sixty-four patients had never received ERT or any GD-specific treatment before their first dose of velaglucerase alfa or were considered treatment-naïve because they had not received a GD-specific treatment for at least 12 months. The remaining 225 patients were switched to velaglucerase alfa ERT from imiglucerase; in the clinical trials, patients switched to velaglucerase alfa in a timely fashion (i.e., without a break in treatment schedule), but in the treatment access protocol which was initiated during a global shortage of imiglucerase, some patients were switched to velaglucerase alfa following a treatment interruption (information on the duration of treatment interruptions was not collected).

Overall, 37 of 289 patients (12.8%) tested positive for antibodies to imiglucerase at the baseline or screening visit: three patients each in two of the clinical studies (TKT034 and the extension study HGT-GCB-044) and 31 patients in the treatment access protocol (HGT-GCB-058), all of whom were previously treated with imiglucerase [12,13,15].

The longest period of velaglucerase alfa exposure was 386.6 weeks, including time in an extension study. The median duration was 36.4 weeks (interquartile range 26.4–155.4 weeks).

3.1. Development of anti-velaglucerase alfa antibodies

Four (1.4%) of 289 patients tested positive for anti-velaglucerase alfa antibodies after exposure to velaglucerase alfa (Table 1): two of 64 patients who were treatment-naïve at baseline (3.1%) and two of 225 patients switched from imiglucerase (0.9%).

In the two patients who were treatment-naïve at baseline, the anti-velaglucerase alfa antibody titers decreased over time, after they tested positive. Between the first positive test result and the end-of-study assessment in the 3-year-old patient (Table 1), the IgG titer fell from 640 to 40. Between the first positive test and the last positive test in the 26-year-old patient who was in fact only transiently antibody-positive, the IgG concentration fell from 346 ng/mL to 97 ng/mL. The

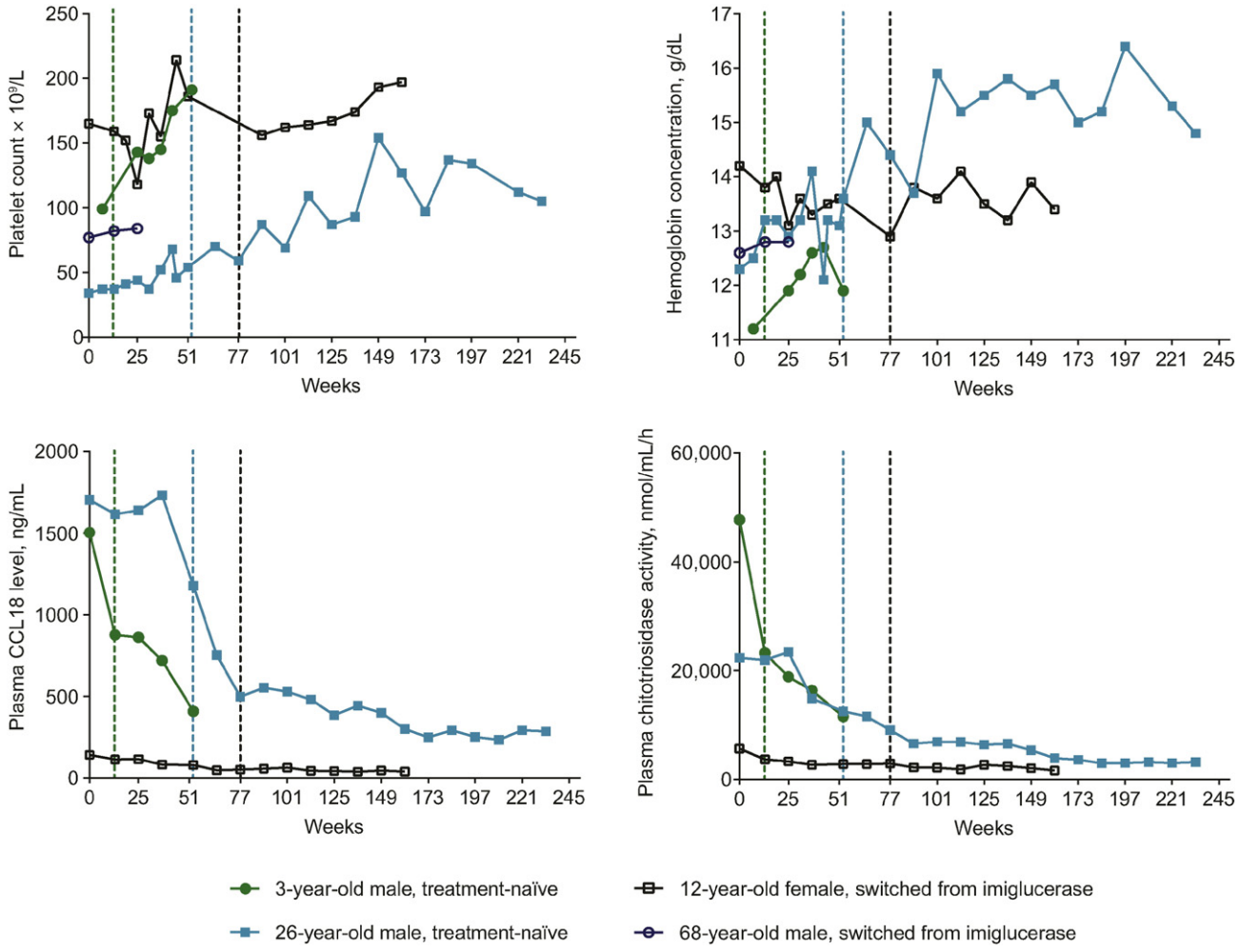

Fig. 2. Platelet count, hemoglobin concentration, CCL18 level and chitotriosidase activity over time in patients who tested positive for anti-velaglucerase alfa antibodies. Some values are the average of two measurements within the same week. 12-year-old female and 26-year-old male were heterozygous for the chitotriosidase gene mutation, so their chitotriosidase measurements have been multiplied by two. Dashed vertical lines mark the time points at which the patients first tested positive for anti-velaglucerase alfa antibodies: 13 weeks for the 3-year-old patient and the 68-year-old patient, 53 weeks for the 26-year-old patient and 77 weeks for the 12-year-old patient.

anti-velaglucerase alfa antibodies detected in the 26-year-old patient had in vitro neutralizing activity.

In the two patients who were switched from imiglucerase, the IgG anti-velaglucerase alfa antibody titers at their first positive tests and at their last study assessments were 258 ng/mL (week 13) and 301 ng/mL (week 25) in the 68-year-old patient, and 1207 ng/mL (week 77) and 8440 ng/mL (week 161) in the 12-year-old patient. The anti-velaglucerase alfa antibodies detected in the 12-year-old patient had in vitro neutralizing activity.

Prior to receiving velaglucerase alfa (at baseline of study TKT034 or HGT-GCB-058), both of the patients who were switching from imiglucerase treatment had high titers of non-neutralizing anti-imiglucerase antibodies. The anti-imiglucerase IgG titers were 583,161 ng/mL in the 68-year-old patient and 240,816 ng/mL in the 12-year-old patient.

Finally, of note, the 68-year-old patient who was switching from imiglucerase treatment was positive for IgE anti-imiglucerase antibodies, in addition to IgG antibodies, at the screening visit for the study HGT-GCB-058.

3.2. Treatment efficacy in anti-velaglucerase alfa antibody-positive patients

Platelet count, hemoglobin concentration, and levels of CCL18 and chitotriosidase all improved during treatment with velaglucerase alfa in the two patients who were treatment-naïve at baseline and they were generally maintained in the two patients who were switched from ERT with imiglucerase. This is consistent with the overall results from the respective clinical study populations, HGT-GCB-044, −058 and −068 [12,15,17]. There were no apparent trends suggestive of clinical deterioration after anti-velaglucerase alfa antibodies were detected (Fig. 2).

3.3. Adverse events in anti-velaglucerase alfa antibody-positive patients

No infusion-related AEs were reported for any of the four patients who became positive for antibodies to velaglucerase alfa. One patient (12-year-old switch patient) received paracetamol during the extension study HGT-GCB-044 as pre-medication to prevent possible infusion reactions. Two patients did not receive any pre-medications at any time. Data on concomitant medication use were not collected for the fourth patient (68-year-old switch patient).

Three of the four patients experienced at least one TEAE; a total of 18 non-serious AEs were reported that were considered neither possibly nor probably related to the study drug (Supplementary Table 1). One patient had no TEAEs (68-year-old switch patient who tested positive after 13 weeks and received the last study infusion in week 33).

None of these patients discontinued from study participation due to an AE.

3.4. Patients with cross-reactive anti-imiglucerase antibodies

Across the velaglucerase alfa clinical studies, 13 of 333 patients were found to have anti-imiglucerase antibodies that were cross-reactive with velaglucerase alfa (although not all patients in the trials were tested for anti-imiglucerase antibodies, of the 289 patients with post-baseline follow-up antibody data, 11 patients were found to have cross-reactive anti-imiglucerase antibodies). Of these 13 patients, one patient was treatment-naïve at the baseline of study HGT-GCB-039 and became positive for both anti-imiglucerase antibodies and anti-velaglucerase alfa antibodies during the 9-month study period in which he received imiglucerase treatment [11]. The remaining 12 patients were participants in the treatment access protocol HGT-GCB-058 who were switching from imiglucerase to velaglucerase alfa treatment; they tested positive for both anti-imiglucerase antibodies and anti-velaglucerase alfa antibodies at the screening visit for HGT-GCB-058 [15]. These 13 patients had no previous exposure to velaglucerase alfa, so positivity for anti-velaglucerase alfa antibodies was attributed to cross-reaction in the assay.

The patient treated with imiglucerase in study HGT-GCB-039 first tested positive at week 13 for IgG anti-imiglucerase antibodies, which cross-reacted in the anti-velaglucerase alfa antibody assay. He remained in the study for another 10 weeks and he was still positive for antibodies to both imiglucerase and velaglucerase alfa at his end-of-study antibody assessment at week 22, despite never having been exposed to velaglucerase alfa. In this patient, the anti-imiglucerase antibodies and anti-velaglucerase alfa antibodies were both neutralizing in vitro; his hematologic variables nevertheless improved in the weeks after he first tested positive. However, he ultimately withdrew consent due to multiple infusion-related reactions [11].

In the treatment access protocol HGT-GCB-058, a total of 37 patients tested positive for anti-imiglucerase antibodies at the screening visit, 12 of whom had cross-reactive antibodies. Thirty-one patients had follow-up antibody data; of these, 10 patients had cross-reactive antibodies (Table 2). The most notable difference between the patients with cross-reactive anti-imiglucerase antibodies and those with non-cross reactive anti-imiglucerase antibodies was the proportion testing positive for neutralizing enzyme activity (Table 2). In any case, there was no apparent difference in the occurrence of TEAEs or infusion-related AEs between ADA-positive switch patients and ADA-negative switch patients in the HGT-GCB-058 study population [15].

4. Discussion

Anti-velaglucerase alfa antibodies were assayed in patients participating in the velaglucerase alfa clinical studies because the

Table 2
Cross-reactivity in anti-imiglucerase antibody-positive patients in the treatment access protocol HGT-GCB-058 (37 patients switched from imiglucerase).

	Cross-reactive anti-imiglucerase antibodies	Non-cross-reactive anti-imiglucerase antibodies	All anti-imiglucerase antibody-positive patients
Screening visit before study			
Patients with available data	12	25	37
Anti-imiglucerase antibodies	12	25	37
Anti-velaglucerase alfa antibodies (cross-reactive)	12	0	12
Neutralizing enzyme activity			
Negative for neutralizing activity	2	23	25
Neutralizing anti-imiglucerase antibodies	9[a]	2	11
Neutralizing anti-velaglucerase alfa antibodies	10[a]	n/a	10
Anti-imiglucerase IgG titer range, ng/mL	528 to 1,829,242	71 to 583,161	71 to 1,829,242
During clinical study			
Patients with available data	10	21	31
Anti-velaglucerase alfa antibodies	9[b]	1[c]	10

[a] One of 10 patients whose sera had neutralizing activity had antibodies that were neutralizing only to velaglucerase alfa.
[b] One patient who tested positive for anti-velaglucerase alfa antibodies at the screening visit (which were cross-reactive anti-imiglucerase antibodies) subsequently tested negative for anti-velaglucerase alfa antibodies during the study.
[c] One patient developed anti-velaglucerase alfa antibodies during the study, after exposure to velaglucerase alfa (the 68-year-old switch patient discussed elsewhere in this report).

development of ADAs is known to occur with biological therapies, including ERTs [21,22]. Theoretically, ADAs may reduce treatment efficacy and lead to allergic and other adverse reactions [21].

Less than 2% of patients exposed to velaglucerase alfa tested positive for antibodies. Velaglucerase alfa's overall seroconversion rate was lower than that reported with imiglucerase (15%), and this is consistent with the ADA results from the head-to-head trial, HGT-GCB-039, that compared velaglucerase alfa with imiglucerase [11,22]. In the HGT-GCB-039 trial, except for the drug itself used to capture and detect antibodies, the analytical platform for analyzing anti-imiglucerase antibodies was identical to the platform for analyzing anti-velaglucerase alfa antibodies. Four patients exposed to imiglucerase developed anti-imiglucerase antibodies whereas none in the velaglucerase alfa treatment group tested positive for ADAs. The major limitation of the HGT-GCB-039 study was the study population size (34 patients). We examined a large group of patients in this analysis, but the antibody testing data was based on analytical methods that were different from those used in studies of imiglucerase (or taliglucerase alfa). At any rate, the agreement between the small controlled study (HGT-GCB-039) and this large data collection is noteworthy.

Among the small group of patients who tested positive for anti-velaglucerase alfa antibodies, there was no apparent correlation between the development of anti-velaglucerase alfa antibodies and AEs or pharmacodynamic or clinical responses, including the two patients with antibodies that were neutralizing in vitro. In general, being positive for velaglucerase alfa ADAs is not a reliable predictor for drug-related hypersensitivity reactions. However, according to a review of real-world global safety data on imiglucerase use, patients who are positive for anti-imiglucerase antibodies may have an increased risk of experiencing a hypersensitivity-type reaction since hypersensitivity symptoms were reported by almost half of antibody-positive patients [22]. Anti-imiglucerase antibodies were generally detected within 6 months of initiating treatment and did not appear to have any effect on efficacy variables [22]. Hypersensitivity reactions have also been observed in patients testing positive for anti-taliglucerase alfa antibodies in clinical trials, including the rare occurrence of anaphylactic reactions [4]. The number of patients developing neutralizing anti-taliglucerase alfa antibodies was too small to determine a relationship with treatment response [4].

Anti-velaglucerase alfa antibody titers were much lower than anti-imiglucerase antibody titers in the two patients who were switched from imiglucerase treatment and developed anti-velaglucerase alfa antibodies. In addition, in the other two patients who developed anti-velaglucerase alfa antibodies, decreasing antibody titers were observed, for which we have no certain explanation; however, supposed 'immune tolerance' with continued regular enzyme replacement has also been observed in patients receiving ERT for Pompe disease and mucopolysaccharidosis I [31,32].

As previously discussed [15], the ADA results of the treatment access protocol (HGT-GCB-058) suggest that neutralizing anti-imiglucerase antibodies are likely to cross-react with velaglucerase alfa.

4.1. Limitations of analysis

Patients were not all exposed to velaglucerase alfa for the same period of time in the clinical studies. Our results suggest that patients can become antibody-positive at any time in the first 18 months of drug exposure, and half of the cohort in the current report received the study drug for less than 9 months.

Because only four patients tested positive for anti-velaglucerase alfa antibodies, we had a very small group in which to evaluate the clinical effect of seroconversion. One of the patients who tested antibody-positive was observed for only 12 weeks after the first positive test result, so the evaluable clinical data were particularly limited in that patient.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.bcmd.2016.03.004.

Authorship contributions

GMP, HB, DEG, HI, AAGT and AZ were investigators in the clinical trials. YQ generated and checked the data. All authors interpreted the data, revised the manuscript and approved the final version.

Conflict of interest disclosures

The authors declare the following potential competing interests: receipt of consulting fee or other remuneration including fee as speaker from a relevant commercial entity (GMP: Shire, Genzyme, BioMarin, Pfizer; HI: Genzyme, Actelion, Shire, JCR, Dainippon Sumitomo; AZ: Shire, Protalix, Genzyme). Current or recent participation in a clinical trial sponsored by a relevant commercial entity (HB and AAGT: Shire; HI: Genzyme, Shire). Research supported by a relevant commercial entity (HI: Genzyme, Dainippon Sumitomo; AZ: Shire). Employee of a relevant commercial entity (Y Qin, Y Qiu and QD: Shire). Assisting in the design of or participating in clinical studies using products manufactured by a relevant commercial entity (AZ: Shire). AZ also declares that Genzyme and Shire are providing grants to his clinic for participation in their respective disease registries (ICGG Gaucher Registry and GOS). DEG has no potential competing interests to declare.

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